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Review

Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors

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Abstract

A systematic meta-analysis of observational studies of melanoma and family history, actinic damage and phenotypic factors was conducted as part of a comprehensive meta-analysis of all major risk factors for melanoma. Following a systematic literature search, relative risks were extracted from 60 studies published before September 2002. Fixed and random effects models were used to obtain pooled estimates for family history (RR = 1.74, 1.41–2.14), skin type (I *vs.* IV: RR = 2.09, 1.67–2.58), high density of freckles (RR = 2.10, 1.80–2.45), skin colour (Fair *vs.* Dark: RR = 2.06, 1.68–2.52), eye colour (Blue *vs.* Dark: RR = 1.47, 1.28–1.69) and hair colour (Red *vs.* Dark: RR = 3.64, 2.56–5.37), pre-malignant and skin cancer lesions (RR = 4.28, 2.80–6.55) and actinic damage indicators (RR = 2.02, 1.24–3.29). Sub-group analysis and meta-regression were carried out to explore sources of between-study variation and bias. Sensitivity analyses investigated reliability of results and publication bias. Latitude and adjustment for phenotype were two study characteristics that significantly influenced the estimates.

Keywords: Melanoma; Meta-analysis; Epidemiology; Review literature; Phenotype; Family history; Actinic damage

1. Introduction

This is the third and last part of a systematic meta-analysis on all published studies until September 30, 2002. All main risk factors for melanoma were investigated and results on naevi and sun exposure were published in previous papers [1,2]. In the present work, family history, actinic damage indicators and the remaining phenotypic factors were considered.

At this time, family history is considered one of the most important risk factors for cutaneous malignant melanoma and researches into potential melanoma susceptibility genes are ongoing [3]. Approximately 8–12% of melanoma patients have a family history [4].

Cutaneous lesions, which may be considered indicators of acute and chronic exposure to UV radiations, were included as photodamage indicators. Actinic keratoses are also called solar keratoses because they indicate that sun damage has occurred. They are precursors of skin carcinomas, which means they can be the first morphological step in the development of skin cancer. It is estimated that up to 10% of active

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lesions will take the next step and progress to squamous cell carcinoma. In particular we analysed solar lentigo, actinic keratosis, solar elastosis and presence of skin carcinoma.

Several phenotypic characteristics were also analysed (hair colour, eye colour, skin colour, presence of freckles and photo-type), trying to investigate interrelationships and associations with the evaluation of adjustment for reciprocal effect.

Most of the evidence relevant to these factors comes from observational studies in humans, and most of these studies were case-control. Several methodological problems may bias the association between these risk factors and melanoma risk. A deep exploration of heterogeneity between study and possible sources of bias has been carried out searching for significant differences by study features, definitions adopted, characteristics of the populations and of the types of analyses.

2. Patients and methods

2.1. Definition of outcome and exposures

The outcome of this systematic meta-analysis was histologically confirmed melanoma.

2.1.1. Family history

Positive family history of melanoma was usually defined as the presence of melanoma in one or more affected first-degree relatives.

2.1.2. Actinic damage

Following "*IARC Monograph on the evaluation of carcinogenic risks to humans; ultraviolet radiation*. Lyon: 1992", we considered as indicators of actinic damage the presence of lesions as solar lentigo, elastosis, actinic keratoses, others objective measurements of actinic damage, as cutaneous microphotography, and personal history of cutaneous tumours, as squamous cell carcinoma (SCC) and/or basal cell carcinoma (BCC).

Definitions adopted by the various authors were classified into two groups:

- Pre-Malignant and Skin-Cancer Lesions (PMSCL): actinic keratoses, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).
- Other Indicators of Actinic Damage (OIAD): solar lentigo, elastosis and indicators found by cutaneous microphotography.

2.1.3. Phenotypic factors

Epidemiologic studies have identified certain phenotypic factors consistently associated with increased risk for the development of malignant melanoma. These factors include photo-type (sun sensitivity: the tendency to burn rather than tan); freckles; blue, green, or gray eyes; blond or red hair and fair complexion.

Fitzpatrick created a standard method for classifying individual skin types, according to their skin colour and burning and tanning responses to sun light exposure. This classification of skin type into four categories, from type I (always burn, never tan) to type IV (never burn, tan easily), is widely used clinically, although the precise questions asked and the responses coded vary between studies [5].

2.2. Methods of analysis

A questionnaire was developed to collect all necessary information about each study, as described in the previous paper on naevi [1]. Definitions of photodamage indicators, of different colours for eye, hair and skin and methods of assessment for photo-type and skin type, were further collected for this meta-analysis.

The summarised RR was estimated by pooling the study-specific estimates using classical fixed effects and random effects models. The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic (Chi) [6]. Sub-group analyses and meta-regressions were carried out to investigate between-study heterogeneity. *P*-values, indicating significance of factors investigated, were obtained with analysis of variance models in SAS with PROC GLM [7], considering the weights of the random effects models [8]. Heterogeneity was investigated looking at all possible factors concerning the type of study, the analysis, the exposure and the features of the population, which could influence the estimates. Studies conducted in several different populations, at substantially different latitudes, were not included in the heterogeneity analysis that evaluated latitude. Sensitivity analysis was conducted to evaluate inclusions criteria and influence of individual studies. Publication bias was investigated by funnel-plot-based approaches to verify whether it might affect the validity of the estimates. *P*-values for fit of the funnel plot in the sensitivity analysis published by Copas and Shy [9], *P*-values for the rank correlation test proposed by Begg (Sperman's *rho* values) [10] and *P*-values for Egger's weighted-linear regression method were presented [11].

Mixed effects models were used in SAS with PROC MIXED [7] to take into account variability within study in the sensitivity analysis [12]. Chen [13] presented estimates separately for the four body sites, and not raw data. The four estimates being very similar with no indication of heterogeneity, a weighted average of the four estimates was included for the main analysis. This decision was made in order not to give too much weight to this study but it was evaluated in the sensitivity analysis. Random effects models with

restricted maximum likelihood estimates were applied thus that the resulting estimate for the between-study variance is identical to the iterated DerSimonian-Laird estimator [8,12].

3. Results

3.1. Selection of articles

Data searches were conducted on Medline (National Library of Medicine, Bethesda USA), using the PubMed interrogation interface, and EMBASE (Elsevier Science, Amsterdam, Holland) using OVID, as in the meta-analysis on naevi count [1]. The reference lists of the retrieved articles and preceding reviews [14,15] on the topic were also checked. No language or time restrictions were applied.

Primary inclusion criteria, developed for the selection of all relevant articles, consider original independent papers that provided necessary information to calculate the estimates. Furthermore it was essential that the populations studied were homogeneous, at least regarding the main risk factor for melanoma. Thus, as in the previous meta-analyses, studies [16,17] conducted exclusively on young subjects (aged less than 19 years) with melanoma were excluded because they were few in number and melanoma in children and adolescents is very rare, very often arises in giant nevus with a different pathology and have completely different risk factors, mainly genetic [18]. Moreover, studies did not include only cases of palms, plantar foot and vulva, since a distinct aetiology for such non sun-exposed sites is suggested [19]. Cockburn [20] presented data from a case-controls study on couple of twins and the estimates, for all phenotypic factors, were presented separately for homozygous and heterozygous. This last study was excluded from the main analysis because it was very different from the other studies but this choice has been evaluated in the sensitivity analysis.

Wide inclusion criteria were chosen in order to start from the premise of using as much data as possible. This allowed us more data to closely investigate possible heterogeneity, the key issue of this meta-analysis. Inclusion and exclusion of single studies was evaluated in the sensitivity analysis to investigate their influence on the pooled results and to exclude potential biases.

Most results were for all subjects, combining sexes; some of them presented results separately for women and men with no combined data. They were used in that form, producing a number of independent data sets higher than the number of studies included in the meta-analysis.

3.2. Study characteristics

An overview of the 60 studies included in the analysis (for a total of 28,157 cases) are given in Tables 1a and 1b. Thirty-three studies were carried out in European countries, 20 in North America, four in Australia, one in Argentina, one in Brazil and one in Israel; two were cohort studies (all dealing with Pre-Malignant and Skin-Cancer Lesions), 57 case-control studies and one a nested case-control study.

3.2.1. Family history

Fourteen eligible independent case-control studies, which evaluated family history and risk of melanoma in all body, were determined (Fig. 1). One study, Green [21], also collected information on second-degree relatives, while Holly [22] did not indicate the degree of relationship. Estimates and some information on three papers [23–25] were obtained from the meta-analysis on individual data published by Ford [14]. In Swerdlow [24], controls did not have any subject with family history, therefore 0.5 was added at each cell of the 2×2 table used for calculation of the estimates [26].

The fixed effects model was used to pool the estimates because between-study heterogeneity was not significant (Chi = 14.08, degree of freedom (d.f.) = 13, $P = 0.37$). The pooled estimate indicated a highly significant association between family history and melanoma (Table 2).

Three papers were excluded on grounds of the inclusion criteria. When the papers written by Youl [17] and Whiteman [16], which presented results only for melanoma in children or adolescents, were included, pooled RR increased but not significantly: 1.86 (95% CI: 1.49; 2.33). When the paper published by Green [27], which analysed only acral melanoma was added, the pooled RR did not change noticeably: 1.79 (95% CI: 1.46; 2.20).

Copas and Shy ($P = 0.21$), Begg's test ($P = 0.44$) and Egger tests ($P = 0.23$) gave no indication of publication bias.

3.2.2. Actinic damage indicators

Sixteen independent papers, on thirteen case-control studies (Moore [28] is a nested case-control study) and three cohort studies, were found for indicators of actinic damage. One of the cohort studies [29] presented results separately for women and men. Definitions used by the authors of the papers were very mixed. By two of them, Osterlind [30] and Holman [31], the extent of actinic damage was measured by a technique (cutaneous microphotography) that takes an impression of the skin texture and it is graded using a microscope. Other works adopted much more rough definitions quantifying lentigines with very broad categories, as "Any" *vs.* "None".

Table 1a
Characteristics of the studies included in the main analysis with the indication of RRs available

First author, PY	Country	Study design	No. cases	No. controls	Cases source	Controls source	PMSCL	OIAD	FH	E	H	S	PT	FR
Gellin, 1969 [78]	USA	CC	79	1037	Hosp	Hosp				X	X	X	X	
Klepp, 1979 [79]	Norway	CC	78	131	Hosp	Hosp								X
MacKie, 1982 [80]	Scotland	CC	113	113	Hosp	Hosp							X	
Beral, 1983 [81]	Australia	CC	287	574	Hosp	Pop					X	X		
Lew, 1983 [82]	USA	CC	111	107	Hosp	Other				X	X		X	
Elwood, 1984 [83]	Canada	CC	595	595	Pop	Pop				X	X	X	X	X
Graham, 1985 [45]	USA	CC	404	521	Hosp	Hosp				X	X	X		
Green, 1985 [21]	Australia	CC	183	183	Pop	Pop	X	X	X	X	X	X		X
Dubin, 1986 [84]	USA	CC	1103	585	Hosp	Hosp	X		X	X	X	X		X
Elwood, 1986 [36]	UK	CC	83	83	Hosp	Hosp				X	X		X	X
Holman, 1986 [85]	Australia	CC	507	507	Pop	Pop	X	X	X	X	X	X		
Swerdlow, 1986 [24]	Scotland	CC	180	197	Hosp	Hosp			X					
Ammannatti, 1987 [86]	Italy	CC	104	104	Hosp	Hosp				X	X	X	X	
Bell, 1987 [87]	UK	CC	268	1577	Hosp	Hosp				X	X			
Cristofolini, 1987 [88]	Italy	CC	103	205	Hosp	Hosp			X	X	X	X		
Holly, 1987 [89]	USA	CC	121	139	Hosp	Hosp	X		X	X	X			X
Bain, 1988 [90]	USA	N CC	98	190	Pop	Pop					X	X		
Osterlind, 1988 [30]	Denmark	CC	474	926	Pop	Pop		X	X	X	X	X		X
Garbe, 1989 [91]	Germany	CC	200	200	Hosp	Hosp		X					X	
MacKie, 1989 [34]	UK	CC	280	280	Pop	Hosp			X				X	X
Beitner, 1990 [49]	Sweden	CC	523	505	Hosp	Pop				X	X		X	
Elwood, 1990 [41]	UK	CC	195	195	Pop	Hosp					X	X		X
Grob, 1990 [92]	France	CC	207	295	Hosp	Pop					X	X		
Augustsson, 1991 [93]	Sweden	CC	121	378	Pop	Pop				X	X		X	
Halpern, 1991 [33]	USA	CC	105	181	Hosp	Pop		X		X	X			X
Lindelof, 1991 [29]	Sweden	Co	15	1973[a]	–	–	X							
Weiss, 1991 [94]	Germany	CC	204	200	Hosp	Hosp					X			
Marrett, 1992 [37]	Canada	CC	583	608	Pop	Pop		X		X	X	X	X	X
Zaridze, 1992 [95]	Russia	CC	96	96	Hosp	Visit to h.						X		X
Zanetti, 1992,98 [96,97]	Italy	CC	260	416	Pop	Pop				X	X		X	
Dunn-Lane, 1993 [98]	Ireland	CC	100	100	Hosp	Hosp				X	X			

PMSCL, previous skin-cancer lesions; OIAD, other indicators actinic-damage; FH, family history; E, eyes colour; H, hair colour; S, skin colour; PT, photo-type; F, freckles. Ger, Germany; Au, Austria; Sw, Switzerland; Fr, France; Bel, Belgium; Seven Eur C, seven European countries; w, women; m, men; Cohort, cohort study; CC, Case-controls study; N CC, Nested Case-controls study; Hosp, hospital controls; Pop, population controls; Visitors, visitors to the hospital.

[a] Cohort size PD.

From the 16 papers found, we obtained 21 estimates, adjusted for the greater number of confounders, on "pre-malignant and skin-cancer lesions" ($n = 11$) and on "other indicators of actinic damage" ($n = 10$) (Fig. 2(a) and (b)). From these extracted estimates a strong positive association with melanoma was suggested. The calculation for the pooled RR confirmed this indication: 2.96 (95% CI: 2.10; 4.19), for the presence of indicators of actinic damage, considered all together. However, there was a very high value for the Chi-square (Chi = 166.49, d.f. = 20, $P < 0.001$) revealing highly significant heterogeneity. Looking separately at the two main sub-groups of studies, we obtained a very high estimate for "pre-malignant and skin-cancer lesions (PMSCL)", more than twice that calculated for "other indicators of actinic damage (OIAD)" (Table 2). The difference between the two was significant ($P = 0.01$). However between-study heterogeneity, within the two groups, remained highly significant with $P < 0.001$ for both groups (Chi = 44.65 with d.f. = 10 and Chi = 73.76 with d.f. = 9, for PMCL and OIAD, respectively). Heterogeneity decreased considerably for PMSCL ($P = 0.09$) if we exclude two estimates: the highest, Marghoob [32] (RR = 17.00 with 95% CI: 8.68; 33.28), and the lowest, Moore [28] (RR = 0.63 with 95% CI: 0.19; 2.11). The exclusion of these two studies did not change significantly the pooled RR, which remained highly significant (RR = 3.92 with 95% CI: 2.94; 5.23). For OIAD, Halpern [33] presented a very odd estimate. It is the only estimate indicating a protective effect for the indicators of photodamage and the RR was even significant. If we exclude this study from the OIAD subgroup the Chi-square remains highly significant (Chi = 28.22, d.f. = 8, $P < 0.001$) and pooled RR slightly increases (RR = 2.47 with 95% CI: 1.67; 3.66).

The paper written by Green [27] was excluded from the main analysis because it presented results only for acral melanoma. If we include this paper, the pooled RR for PMSCL does not change considerably: 3.95 (95% CI: 2.70; 5.76).

Table 1b
Characteristics of the studies included in the main analysis with the indication of RRs available

First author, PY	Country	Study design	No. cases	No. controls	Cases source	Controls source	PMSCL	OIAD	FH	E	H	S	PT	FR
Herzfeld, 1993 [46]	USA	CC	324	415	Pop	Pop				X	X	X		X
Nelemans, 1993 [53]	Netherlands	CC	141	183	Pop	Pop				X	X	X		X
Autier, 1994 [99]	Bel, Fr, Ger.	CC	420	447	Hosp	Neigh.					X		X	
Garbe, 1994 [100]	Ger, Au, Swi.	CC	513	498	Hosp	Hosp		X			X		X	
Marghoob, 1994 [32]	USA	Co	–	124[a]	–	–	X							
Westerdahl, 1994 [101]	Sweden	CC	400	640	Pop	Pop			X	X	X			X
White, 1994 [39]	USA	CC	256	273	Pop	Pop					X			X
Holly, 1995 [22]	USA	CC	452	930	Pop	Pop			X	X	X	X	X	X
Bataille, 1996 [102]	England	CC	426	416	Pop	Hosp							X	
Chen, 1996 [13]	USA	CC	548	494	Pop	Pop				X	X	X	X	X
Frish, 1996 [103]	Canada	CC	103	533	Pop	Pop	X							
Grulich, 1996 [38]	Australia	CC	242	276	Hosp	Pop + hosp	X	X		X	X			X
Rodenas, 1996 [52]	Spain	CC	105	138	Hosp	Visit to h.				X	X	X	X	X
Dabkowski, 1997 [55]	Poland	CC	74	300	Hosp	Pop				X		X		
Freedman, 1997 [54]	USA	CC	12156	23845	Pop	Pop						X		
Moore, 1997 [28]	USA	CC	69	69	Pop	Pop	X			X	X			X
Tucker, 1997 [104]	USA	CC	716	1014	Hosp	Hosp								X
Lock-Andersen, 1998 [48]	Denmark	CC	168	176	Hosp	Pop				X	X	X	X	
Wolf, 1998 [105]	Austria	CC	193	319	Hosp	Hosp				X	X	X	X	X
Carli, 1999 [106]	Italy	CC	131	174	Hosp	Pop				X	X	X	X	X
Tabenkin, 1999 [107]	Israel	CC	168	325	Pop	Pop			X	X	X	X	X	
Walter, 1990–1999 [25,108]	Canada	CC	583	608	Pop	Pop			X			X		X
Naldi, 2000 [109]	Italy	CC	542	538	Hosp	Hosp		X		X	X	X	X	X
Kaskel, 2001 [110]	Germany	CC	271	271	Hosp	Hosp	X	X	X	X	X		X	X
Landi, 2001[44]	Italy	CC	183	179	Hosp	Pop + hosp				X	X	X	X	X
Loria, 2001 [111]	Argentina	CC	101	249	Hosp	Hosp			X	X	X	X	X	X
Pfahlberg, 2001 [42]	7 Europ countries	CC	603	627	Pop	Pop							X	X
Shors, 2001 [43]	USA	CC	386	727	Pop	Pop					X		X	X
Bakos, 2002 [112]	Brasil	CC	103	206	Hosp	Hosp				X	X		X	X

PMSCL, previous skin-cancer lesions; OIAD, other indicators actinic-damage; FH, family history; E, Eyes colour; H, hair colour; S, skin colour; PT, photo-type; F, freckles. Ger, Germany, Au, Austria; Sw, Switzerland; Fr, France; Bel, Belgium; Seven Eur C, seven European countries; w, women; m, men; Cohort, cohort study; CC, Case-controls study; N CC, Nested Case-controls study; Hosp, hospital controls; Pop, population controls; Visitors, visitors to the hospital.

[a] Cohort size PD.

Copas and Shy ($P = 0.13$) and Egger tests ($P = 0.81$) gave indication of no significant effect of a possible publication bias.

3.2.3. Phenotypical factors

3.2.3.1. Freckles. Thirty-two independent papers, based on only case-control studies (Moore [28] is a nested case-control study), evaluated melanoma risk for high density of freckles. Mackie [34] presented estimates separately for sex. Measurements and classifications of freckles density varied substantially among studies. Classification of freckling varied from 2 to 5 categories; some authors were interested in a classification between people with freckles and those without freckles and others evaluated their intensity with more precise categorization. Some authors asked about freckles after sun or on summertime [13, 28, 35–37]. Some of them used very detailed definitions [23] or diagrams for comparison [38], some others used a general indication of "freckles". Some authors investigated freckles as adult [22, 30], some other as child or teenager [13, 38–40].

Elwood in 1986 [36] and in 1990 [41] published two different estimates, evaluating freckles in adulthood and in childhood. "Freckles in adulthood" is the definition chosen for the main analysis considering more recent information as more reliable. However these estimates presented huge confidence intervals whereas RRs for freckles in childhood were much more precise. Therefore, the choice to include the estimate calculated by Elwood, on freckles as adult, was evaluated in the sensitivity analysis.

In order to reduce the problem of misclassification bias, the estimates extracted are those comparing highest categories *vs.* lowest categories. However, this choice was checked in the sensitivity analysis because many authors consider only two rough dichotomous categories. A further pooled estimate was calculated reducing to a dichotomy the larger number of groupings. Thus, it was possible to make a comparison with results from the meta-analysis on individual data published by Bliss [15]. Many of the papers presented both estimates: for dichotomous exposure and for a higher number of

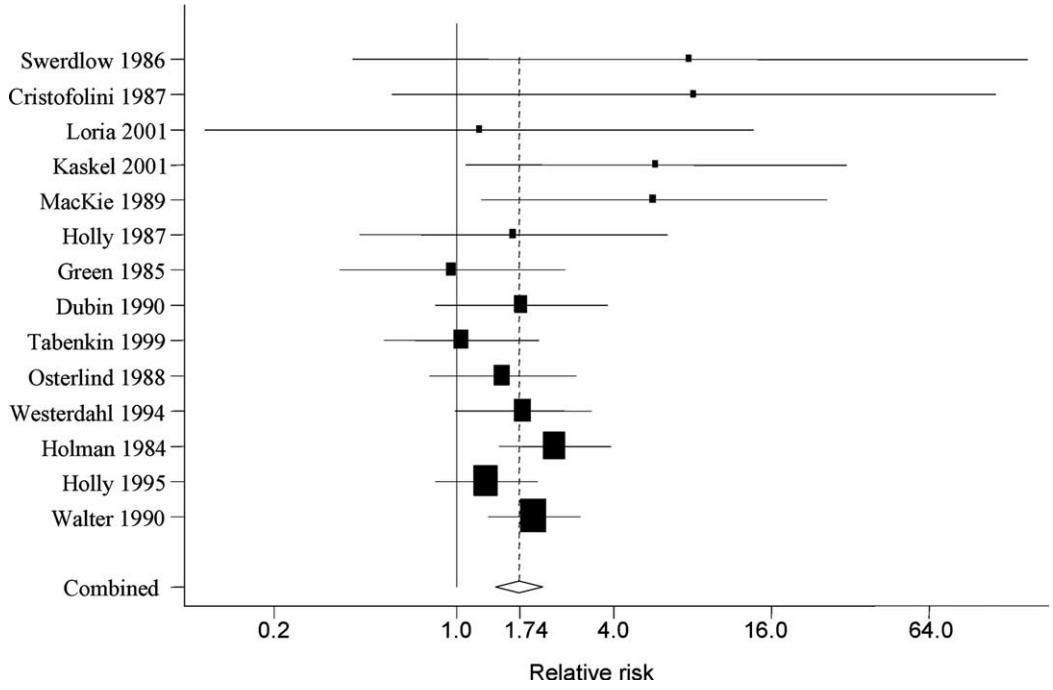

Fig. 1. RR and 95% CIs* of Melanoma risk for family history of melanoma. *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

Table 2

Risk factors	Categories	RR and 95% CI	Heterogeneity Chi-square *P*-value
Family history:	Yes *vs.* No	1.74 (1.41, 2.14)	0.368
Actinic damage indicators:	Pre-malignant and skin-cancer lesions *vs.* No	4.28 (2.80, 6.55)	< 0.001
	Other indicators *vs.* No	2.02 (1.24, 3.29)	<0.001
Density of freckles	High *vs.* Low	2.10 (1.80, 2.45)	<0.001
Phototype	I *vs.* IV	2.09 (1.67, 2.58)	0.002
	II *vs.* IV	1.84 (1.43, 2.36)	<0.001
	III *vs.* IV	1.77 (1.23, 2.56)	<0.001
Eye colour	Blue *vs.* Dark	1.47 (1.28, 1.69)	<0.001
	Green *vs.* Dark	1.61 (1.06, 2.45)	<0.001
	Hazel *vs.* Dark	1.52 (1.26, 1.83)	0.499
Hair colour	Red *vs.* Dark	3.64 (2.56, 5.37)	<0.001
	Blond *vs.* Dark	1.96 (1.41, 2.74)	<0.001
	Light brown *vs.* Dark	1.62 (1.11, 2.34)	<0.001
Skin colour	Light *vs.* Dark	2.06 (1.68, 2.52)	<0.001

categories. When the former was not published it was calculated from the raw data.

Looking at the forest plot (Fig. 3), it can be seen that the risk for high density of freckles is twice greater than the risk of having no or sparse freckling. In fact the pooled estimate, obtained from the random effects model, indicated high density of freckles as a highly significant risk factor (Table 2). However, the between-study heterogeneity was considerable (Chi = 93.45; d.f. = 32; $P < 0.001$).

Interesting results, similar to heterogeneity findings on sunburns and chronic sun exposure published in the previous meta-analysis [2], were found from meta-regression analysis on freckles density. ''Latitude'' significantly explained variability among the estimates: at higher latitudes the risk for having high freckles density was significantly greater than at lower latitude ($P = 0.03$, Fig. 8).

Bliss [15] found that freckles density at young ages defines a more extreme phenotypic risk group than at

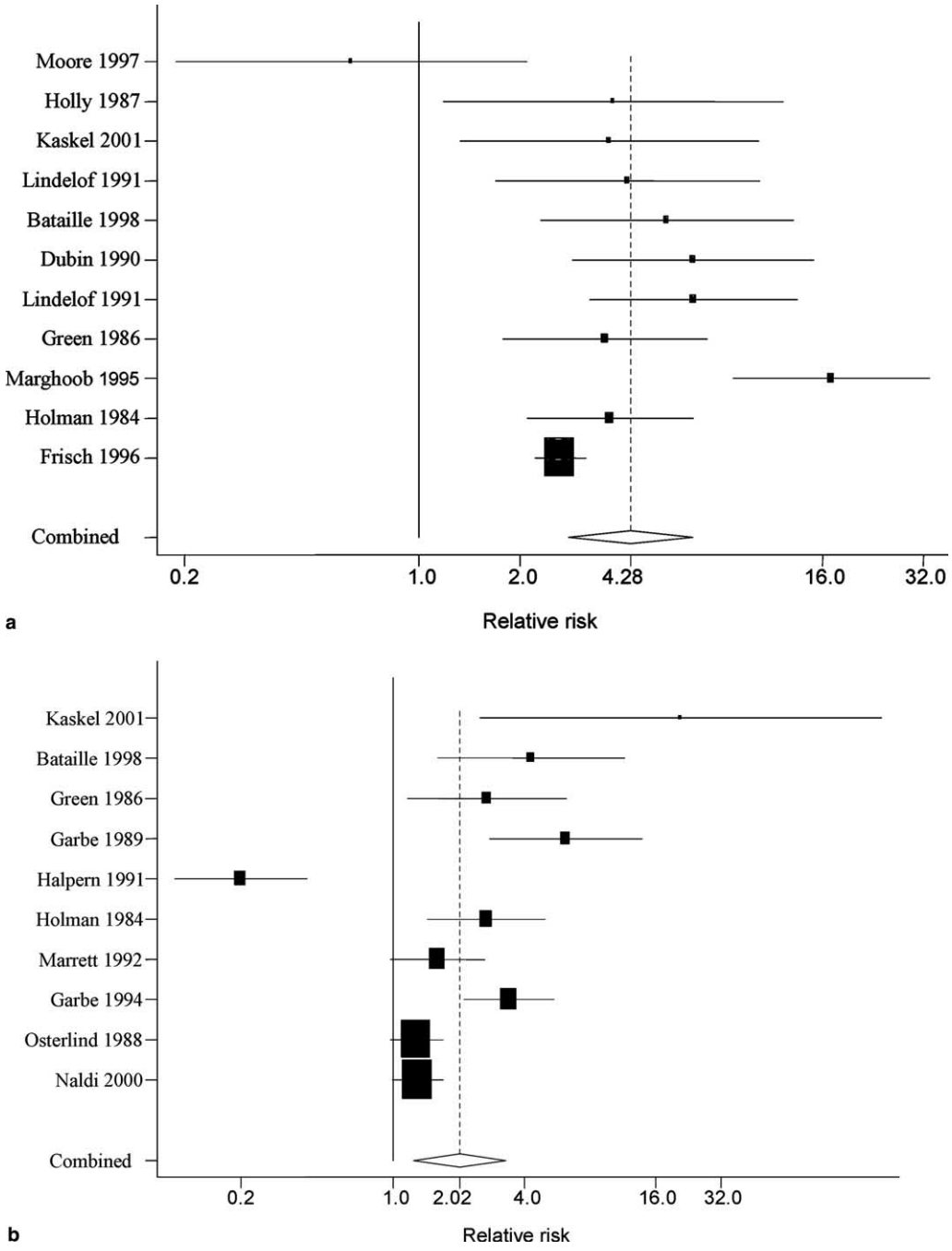

Fig. 2. (a) RR and 95% CIs* of Melanoma risk for pre-malignant and skin-cancer lesions. (b) RR and 95% CIs* of Melanoma risk for other indicators of actinic damage. *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

older ages. In this analysis, we were unable to analyse the interaction with age. The only observation that we could make regards the influence of adjustment for some confounders and on the reference period considered, when reported (*e.g.*, "Adulthood", "Young adult", "Before age of 20" and "Childhood"). Few studies ($n = 9$) evaluated the risk for high density of freckles before age of 25, but for this subgroup of studies the pooled RR (RR = 2.32; 95% CI: 1.72; 3.14) was higher but not very different from the RR calculated for high density of freckles in adulthood (RR = 2.05; 95% CI: 1.71; 2.46), furthermore estimates adjusted for age and sex did not significantly differ from unadjusted ones ($P = 0.24$). As in the meta-analysis published by Bliss [15], phenotype and photo-type did not seem to play an important role because adjustment for these confounders did not influence significantly the estimates for freckles density ($P = 0.46$ and 0.51, respectively). When the dichotomous exposure was considered ("None/Few" *vs.* "Many/Some" freckles), we obtained

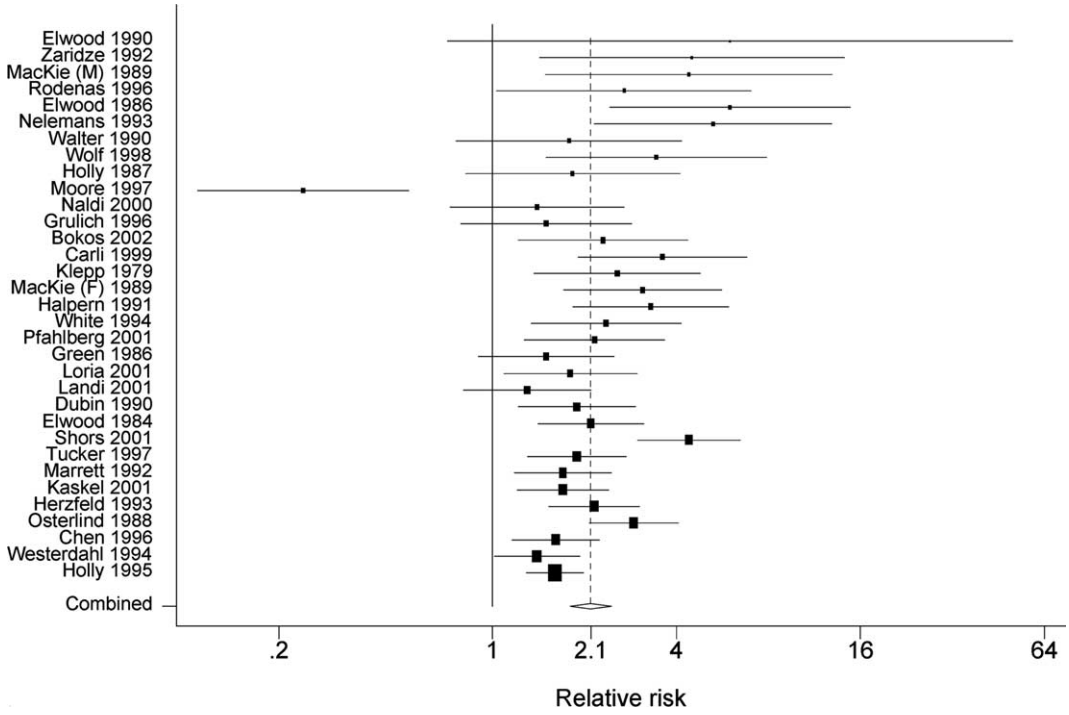

Fig. 3. RR and 95% CIs* of Melanoma risk for high freckle density *vs.* low density. *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

results very similar to the ones obtained in the meta-analysis on individual data published by: the subjects with medium–high density of freckles were at high-risk, compared to subjects with medium–low density of freckles (RR = 2.06; 95% CI: 1.83; 2.32). Between-study heterogeneity was still very elevated (Chi = 92.43; d.f. = 32; $P < 0.001$).

As mentioned previously, Elwood in 1990 [41] and in 1986 [36] presented two estimates concerning freckles in adulthood and in childhood and the first one was included in the main analysis. When estimates evaluating freckles in childhood were considered for the pooled RR, results did not change notably (RR = 2.12; 95% CI: 1.82; 2.47). Pfahlberg [42] published estimates for ephelides (freckles) on arms and on face separately. In order to be conservative, RR that referred to face was chosen because lower than the one on arms. However if the highest one is chosen the pooled estimate did not change significantly (RR = 2.16; 95% CI: 1.84; 2.53). One study [28] presented a really odd result: a highly significant protective effect of high density of freckles. However, the authors did not publish RR estimates but only the percentage of cases and controls and they investigated a different endpoint: freckles that changed with sun. When we excluded the risk estimate that we calculated from published crude data, ignoring the matching design, again the pooled estimate did not change significantly (RR = 2.17; 95% CI: 1.90; 2.47). However the heterogeneity was reduced by one third, even if it was still highly significant (Chi = 66.12; d.f. = 31; $P < 0.001$). Cockburn [20] published data from a case-controls study on couple of twins. When the estimates, presented separately for homozygous and heterozygous, were included in the analysis again the pooled estimate did not change significantly (RR = 2.10; 95% CI: 1.81; 2.45). The inclusion of the paper published by Green [27], which was excluded because it presented results only for acral melanoma, did not modify the pooled RR for high density of freckles: 2.07 (95% CI: 1.78; 2.40). When papers published by Youl [17] and Whiteman [16], excluded because they evaluated risk on younger subjects, were incorporated again the pooled RR did not change significantly: 2.10 (95% CI: 1.80; 2.45). Considering the four estimates calculated by Chen [13], as they are, and applying a mixed model that took into consideration within study correlation, the pooled RR again did not show any considerable change: RR = 2.11, (95% CI: 1.78; 2.50). Looking at the weights of the study estimates it can be seen that there was a very influential study: [22]. The weight of the estimate extracted from this study was greater than 80. However the pooled RR, calculated with the exclusion of it, did not change very much (RR = 2.13; 95% CI: 1.81; 2.51).

A slight suggestion of a possible effect of publication bias was found for freckles ($P = 0.07$). The publication probability became one (no bias) when we added only three unpublished studies and, in this case, the pooled RR somewhat decreased but it remained highly significant (RR = 2.05; 95% CI: 1.62; 2.60). Similar results

were obtained with Begg's method ($P = 0.01$) and linear regression analysis on the funnel plot (Egger's method) ($P = 0.10$). The "Trim and fill" analysis suggested that the number of missing studies may be eight and their inclusion would lead to a slightly lower pooled estimate (RR = 1.82; 95% CI: 1.55, 2.14).

3.2.3.2. Skin photo-type. Twenty-nine independent case-control studies and 30 data sets (Mackie [34] presented estimates separately for sex) were retrieved (Fig. 4). Some papers evaluated "skin type" using Fitzpatrick classification, while others presented definitions based on reaction of the skin after sun exposure. Marret [37] published two estimates looking at "skin's reaction to strong sunlight after the first summer exposure" and "after repeated exposures". The second one was chosen because it was considered more appropriate to have a reliable estimate for skin phototype. Shors [43] and Landi [44] published two estimates looking at "Tendency to burn or skin reaction" and "Ability to tan". The first one was chosen because it should be easier to remember and the risk of misclassification should be lower. These choices were discussed in sensitivity analysis. Eight papers presented also dichotomous estimates, whereas 23 papers considered skin type as an ordinal categorical variable.

When ordinal categorical estimates were considered an increasing trend in melanoma risk, with decreasing skin type levels, was found (Table 2). Collapsing the categories, the pooled relative risk showed that people with skintype I or II are also at significantly higher risk than people who never burn and tan easily (RR = 2.99 and 95% CI: 1.75, 5.12). Heterogeneity was found to be significant ($P < 0.001$). None of the study characteristics, analysed to investigate heterogeneity, was significantly associated with the variability between the estimates. Even if adjustment for phenotype was not significant in explaining variability among the estimates, it was observed a reduction in the pooled RR calculated on the adjusted estimates. Pooled RR for skintype I of estimates not adjusted for phenotype was RR = 2.67 (95% CI: 1.88, 3.79) whereas the pooled RR of adjusted estimates was RR = 1.67 (95% CI: 1.36, 2.03), suggesting an association between these host factors.

When the excluded definitions proposed by Landi [44], Shors [43] and Marrett [37] were included for the calculation of the pooled estimates, the RRs for skintype I, II and III did not change significantly: RR = 1.95 with (95% CI 1.59, 2.39), RR = 1.80 with (95% CI 1.43, 2.27) and RR = 1.64 with 95% CI (1.19, 2.26), respectively. The paper published by Green [27], which was previously excluded because it presented results only for acral melanoma, was included in the sensitivity analysis and its inclusion did not change the results considerably: RR = 2.12 (95% CI: 1.73; 2.61), RR = 1.87 (95% CI: 1.46; 2.38) and RR = 1.81 (95% CI: 1.27; 2.56) for skintype I, II and III, respectively. When we integrated papers published by Youl [17] and Whiteman [16], which were not considered because they analysed only melanoma in children and adolescents, again the pooled RR did not change significantly: RR = 2.08 (95% CI: 1.69; 2.56), RR = 1.84 (95% CI: 1.43; 2.36) and

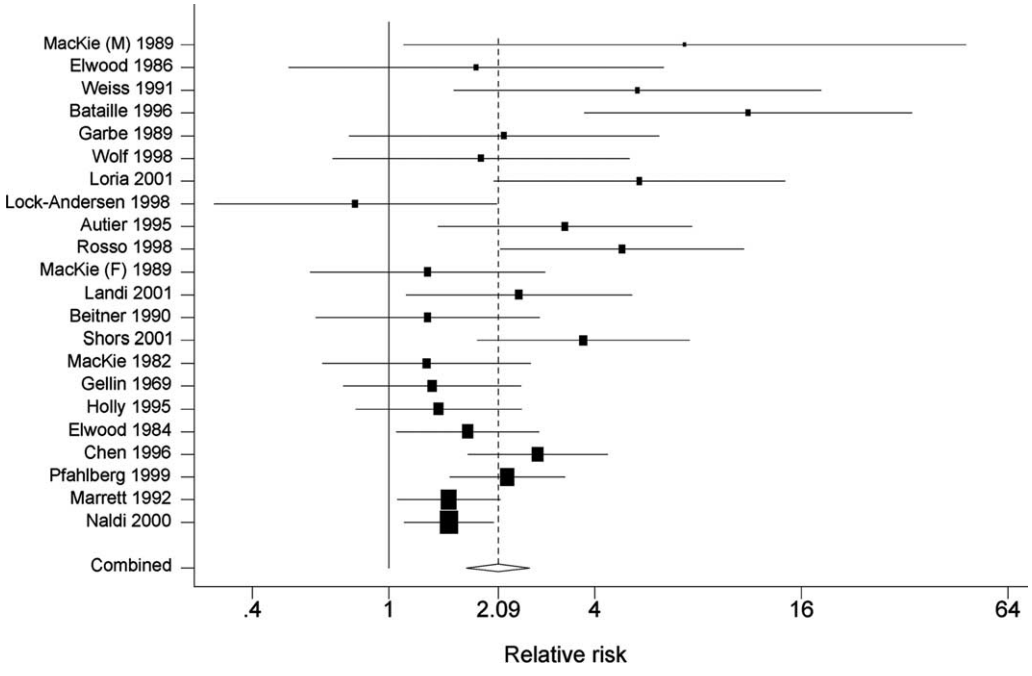

Fig. 4. RR and 95% CIs* of Melanoma risk and skintype I. *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

RR = 1.78 (95% CI: 1.24; 2.56) for skintype I, II and III, respectively. The inclusion of the four estimates published by Chen [13], as they were, did not produce different results: RR = 2.10 (95% CI: 1.66; 2.64), RR = 1.84 (95% CI: 1.41; 2.39) and RR = 1.66 (95% CI: 1.16; 2.39), for skintype I, II and III, respectively.

There was a suggestion for publication bias for skin photo-type I with Begg's method ($P = 0.03$) and linear regression analysis on the funnel plot (Egger's method) ($P = 0.03$). The "Trim and fill" analysis suggested that the number of missing studies may be three and their inclusion would lead to a slightly lower pooled estimate (RR = 1.90; 95% CI: 1.51, 2.39).

3.2.3.3. Eye colour. Thirty-seven eligible papers published information on eye colour and melanoma from independent case-control studies (Moore [28] is a nested case-control study). Thirty-eight data sets were analysed, because Graham [45] published estimates separately for men and women. Hezerfeld [46] presented estimates only for men and Holly [22] only for women.

Classification of eye colour was usually in three qualitative categories, "Black/Brown", "Green/Grey/Hazel" and "Blue/Grey", but some authors included also "Hazel" and others used only broader category as "Light" *vs.* "Dark" eye colour. It was difficult to define a single category of colour at consistent higher risk, thus four pooled estimates were calculated. One for a broader classification as "Fair *vs.* Dark/Brown" eye colour, calculated to reduce to a dichotomy the larger number of groupings (34 data sets, Fig. 5). Three subgroups of studies were also analysed, for more specific colour: "Blue or Blue/Grey" (29 data sets), "Green or Green/Grey" (12 data sets) and "Hazel or Hazel/Grey" *vs.* "Dark" (8 data sets).

The pooled estimate indicated that subjects with fair eyes were at significantly higher risk than subjects with dark eyes (RR = 1.62; 95% CI: 1.44; 1.81). When estimates for more defined colours were considered the pooled RR did not change considerably (Table 2).

Even if the methods of assessment and the categories used to classify eye colour were quite consistent, a considerable between-study heterogeneity was indicated by the high significant value of the Chi-square for "Fair", "Blue" and "Green" ($P < 0.001$), but not for "Hazel" ($P = 0.51$). Heterogeneity was investigated considering the widest group of estimates ("Light *vs.* Dark"), but none of the factors considered significantly explained between-study variability. To explore influence of adjustment of the estimates, the more definite colour definitions were considered because they were fully adjusted. Adjustment for phenotype explained some variability between the estimates for "Blue *vs.* Black", which was the widest subgroup of estimates. In Fig. 9, indication of adjustment was presented for each estimate comparing "Blue *vs.* Black" eye colour. Meta-regression indicated an almost significant difference between adjusted and not adjusted estimates for phenotype ($P = 0.07$). Similarly to the results obtained in the meta-analysis published by Bliss [15], the pooled RR

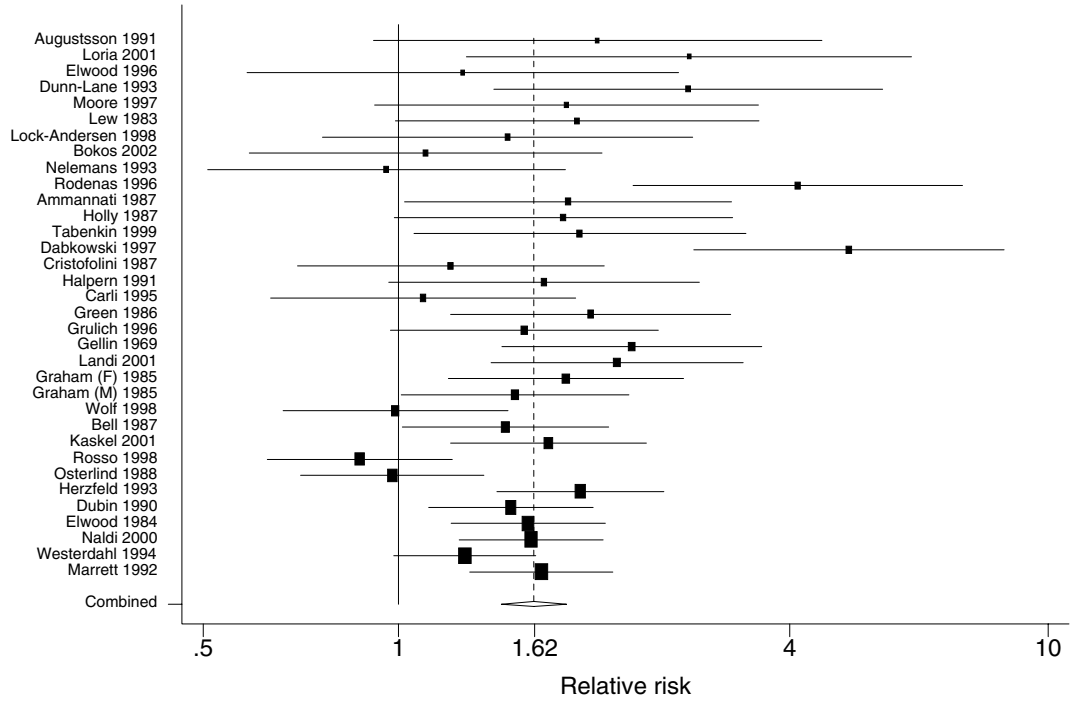

Fig. 5. RR and 95% CIs* of Melanoma risk and eye colour ("Light" *vs.* "Dark"). *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

on estimates for "Blue" eyes, adjusted for phenotype (hair colour, freckles, skin colour), was lower (RR = 1.26, 95% CI: 1.11; 1.43) than unadjusted estimates (RR = 1.60, 95% CI: 1.30; 1.95). This suggested a considerable correlation between these host factors. Furthermore, heterogeneity in the subgroup of estimates adjusted for phenotype, was not any more significant ($P = 0.45$), whereas for estimates not adjusted for phenotype was still highly significant ($P < 0.001$). This may suggest that a lower RR for eye colour, by itself, should be considered.

When the four estimates published by Chen [13], for the four different body sites, were included in the analysis, as they were, the pooled relative risk for "Light" eye did not change significantly (RR = 1.65, 95% CI: 1.47, 1.85). Evaluating the effect of inclusion criteria, estimates published by Cockburn [20], which presented separately for homozygous and heterozygous, were included in the analysis and again the pooled estimate for "Blue" eye colour was slightly reduced (RR = 1.48; 95% CI: 1.29; 1.70). When we included the two studies [16,17], excluded from the main analysis for the inclusion criteria, the pooled RR for "Blue" eyes decreased again, even if it remained significant (RR = 1.46 with 95% CI: 1.27; 1.67); the pooled RR for "Green" and "Hazel" eyes did not change considerably (RR = 1.59 with 95% CI: 1.06–2.39 and RR = 1.49 with 95% CI: 1.77–1.49, for "Green" and "Hazel", respectively).

No indication for publication bias was found for "Blue", "Green" and "Hazel" eyes colour but there was a slight suggestion for "Light" eyes ($P = 0.07$). However with seven more papers, as suggested by Trim and Fill method, the pooled RR did not change significantly: RR = 1.45 (95% CI: 1.27, 1.64).

3.2.3.4. Hair colour. There were 45 case-control studies (Weinstock [47] and Moore [28] were nested case-control studies) and 46 data sets, because Graham [45] presented estimates separately for sex. Definitions and assessments varied considerably between studies. In some studies the interviewer was a dermatologist or trained physician, in others a general questionnaire was used; some authors referred to independent colour or density charts, for classification of pigmentation characteristics, whereas in others, broad categorical rating was used. Some studies asked about a natural hair colour, others simply about hair colour; some questions were about adult hair colour (at time of interview), others about hair colour at 20 years or in childhood. Lock-Anderson [48] and Elwood [36] presented two estimates, as adult and as child; hair colour as child was chosen because the majority of the studies considered hair colour before age of 20. Classification of hair colour was quite similar across studies. The majority of the authors considered three main categories for hair colour: "Black or Brown", "Blond, Fair or Auburn" and "Red or Blond-Red",

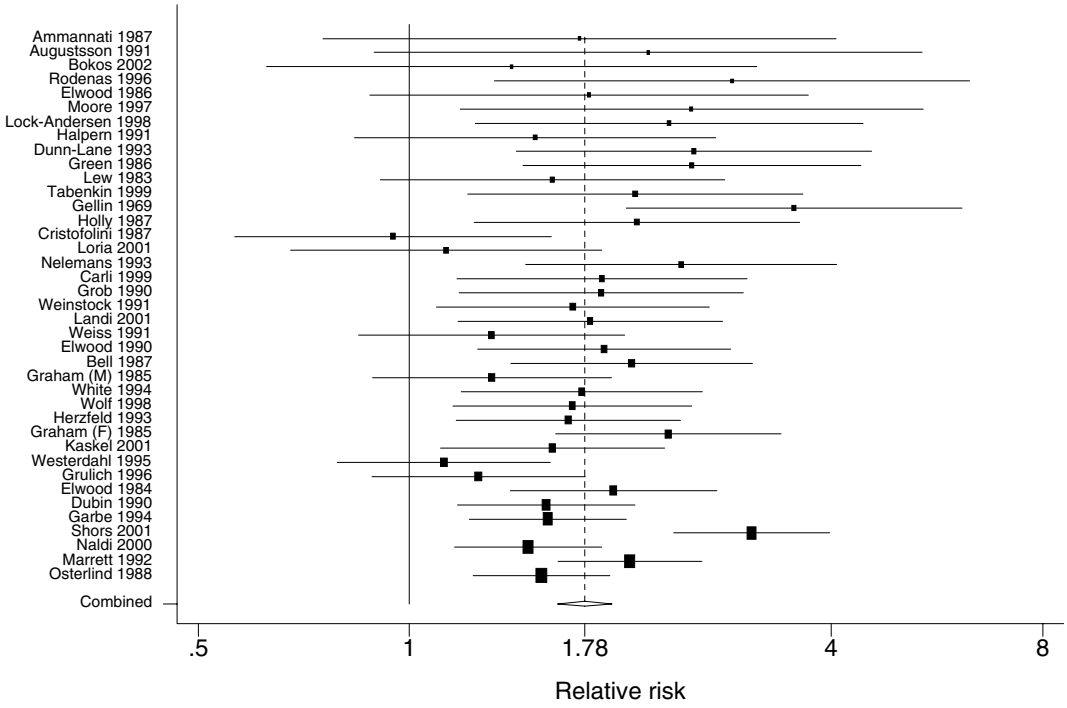

Fig. 6. RR and 95% CIs* of Melanoma risk and hair colour ("Light" *vs.* "Dark"). *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

but some authors used only broader category as "Light" *vs*. "Dark" hair colour. Thus four pooled estimates were calculated. One for a broader classification as "Light" *vs*. "Dark or Brown" hair, calculated reducing to a dichotomy the larger number of groupings (39 studies, Fig. 6), and three other groups of estimates were analysed for more specific colours: "Red" (23 studies), "Blond or Fair/Blond or Auburn" (28 studies), "Light Brown" (17 studies).

The pattern of risk of melanoma by hair colour was reasonably consistent across studies and "Light" hair was shown to be significantly associated to melanoma. In the vast majority of the studies statistical significance was reached (Fig. 6).

The pooled estimate indicated that subjects with "Red" hair colour were at significantly higher risk than subjects with "Dark" hair colour (Table 2). Subjects with "Blond" and "Light Brown" hair colour were also at a significantly higher risk than subjects with "Dark" hair colour, even if the RR was lower than that for "Red" colour. A very high between-study heterogeneity ($P < 0.001$) was also found for all these comparisons. A similar estimate was found considering "Blond/Red" *vs*. "Dark", but heterogeneity was lower (RR = 2.09, 95% CI: 1.75; 2.48, Chi-square $P = 0.08$). Collapsing the categories "Blond, Red and Light Brown", a significantly higher risk was found for "Light" *vs*. "Medium Dark, Brown" hair colour (RR = 1.78, 95% CI: 1.63; 1.95).

Heterogeneity was investigated considering the widest group of estimates: "Light" *vs*. "Dark". However to explore influence of adjustment of the estimates, the more definite colour definitions were considered because they were fully adjusted.

Bliss [15] showed higher relative risk for hair colour assessed in younger individuals. In fact, it is possible that melanoma risk is related to hair colour at a younger age, and that hair colour in older individuals is a less accurate measure. However, when we looked at differences between hair colour in childhood and hair colour with the other more general definitions, we did not find any significant difference among the estimates. Meta-regression indicated a significant difference between adjusted for phenotype and not adjusted estimates for phenotype ($P = 0.02$). The pooled RR for "Red or Blond/Red" hair colour on estimates adjusted for phenotype (eye colour, freckles, skin colour) was lower (RR = 1.86, 95% CI: 1.41; 2.45) than on unadjusted ones (RR = 3.32, 95% CI: 2.52; 4.37). This suggested a considerable correlation between these host factors. Furthermore heterogeneity analysis, in the subgroup of adjusted estimates, was lower ($P = 0.05$), whereas for unadjusted was still highly significant ($P < 0.001$). This suggested that a lower RR should be considered as more reliable for hair colour.

Beitner [49] presented very high estimates for "Red" (RR = 69.5 with 95% CI: 33.8; 142.7), "Blond" (RR = 74.4 with 95% CI: 45.8; 120.8) and "Light Brown" hair colours (RR = 26.1 with 95% CI: 16.1; 40.9). If we exclude this study from the analysis, the pooled RR decreased for "Red" (RR = 2.86 with 95% CI: 2.26; 3.62), "Blond" (RR = 1.65 with 95% CI: 1.40; 1.95) and "Light brown" hair colour (RR = 1.34 with 95% CI: 1.13; 1.58) but it remained considerable. When we included the two studies [16, 17], that were excluded from the main analysis for the inclusion criteria, the pooled RR decreased again for "Red", even if it remained significant (RR = 2.57 with 95% CI: 2.08; 3.17), whereas it did not change significantly for "Blond" hair colour (RR = 1.90 with 95% CI: 1.36; 2.65). Considering estimates published by Chen [13], for the four body parts, as they were published, mixed effects model produced lower but still significant results for "Red" hair (RR = 2.67 with 95% CI: 2.13; 3.35).

No publication bias was suggested for the estimates of "Red", "Blond" and "Light brown" *vs*. "Black" hair colour.

3.2.3.5. Skin colour. The 30 independent papers presented results all acquired from case-control studies (one is a nested case-control study: Weinstock [47]). We obtained 31 data sets, because Graham [45] published estimates separately for sex. Hezerfeld [46] published estimates only on men and Holly [22] and Weinstock [50] only on women. Some studies used previously validated skin colour charts; some used prosthesis and wigmakers's samples whereas others made a simple broad visual assessment. Some authors judged skin colour with scores on a quartile or quintile scale, others considered a rough coding classification as "Dark", "Medium" and "Light". Some papers investigated skin colour presenting estimates for sun-exposed and unexposed body sites (*e.g.*, upper inner arm) and the latter was chosen for the meta-analysis. It is hard to measure skin colour because it exhibits a much narrower colour range than hair or eye colour. Therefore, in order to reduce the problem of misclassification bias, it was decided to include the estimates comparing highest *vs*. lowest categories. However in the sensitivity analysis, a pooled RR was calculated reducing to a dichotomy the larger number of groupings, because many authors considered only two broad categories. Data from the categories defined as "Dark" and "Medium" were collapsed into "Dark/Medium", and data belonging to the categories described as "Light" and "very Light" into the category "Light". Calculations were done on the studies that published at least raw data. Three studies [13, 22, 51] were not included for this dichotomous categorization because they presented only estimates for more categories and no raw data.

ORs for "Light" *vs*. "Dark/Medium", adjusted for the maximum number of confounders, were presented in the forest plot (Fig. 7). As can be seen, the majority

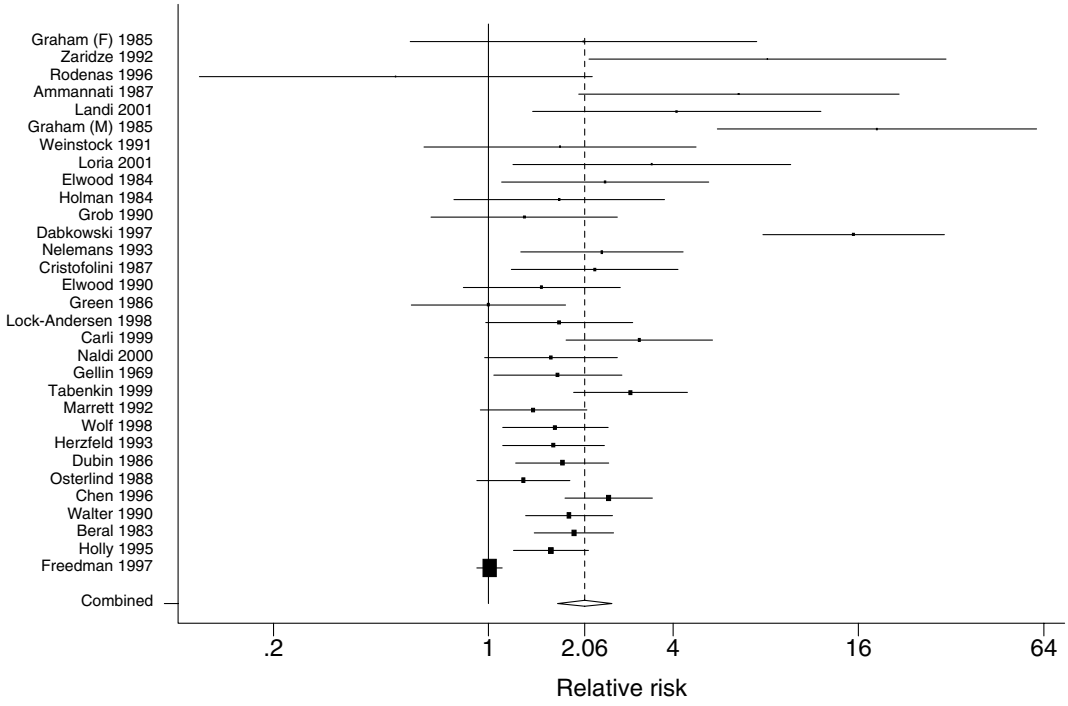

Fig. 7. RR and 95% CIs* of Melanoma risk and skin colour (“Light” *vs.* ”Medium/Dark”). *95% CI were calculated using SE(log RR), estimated from published C.I with the formula proposed by Greenland [6].

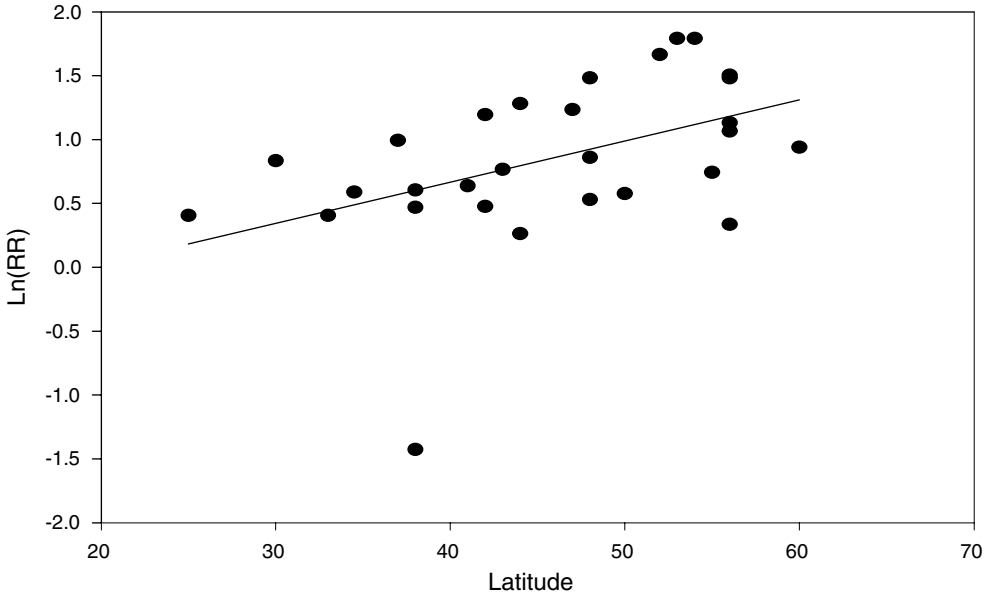

Fig. 8. Ln(RR) for high density of freckles by Latitude.

indicated that people with “Light” skin were at considerable higher risk compared to people with “Dark” skin. Coefficients of the studies were summarized with random effects models, heterogeneity being highly significant ($P < 0.001$), and the pooled relative risk for “Light” skin colour, compared to “Dark”, indicated a significant high risk (Table 2). Pooled RR on the dichotomous exposure, “Light” *vs.* “Dark/Medium”, was very similar to the one comparing adjusted estimates of the highest *vs.* the lowest categories (RR = 1.92 and 95% CI 1.61, 2.28). Chi-square remained highly significant ($P < 0.001$).

Method of classification of skin colour did not seem to explain heterogeneity but it is not easy to evaluate statistically this aspect that is essentially qualitative. The aspect that seemed to explain some variability

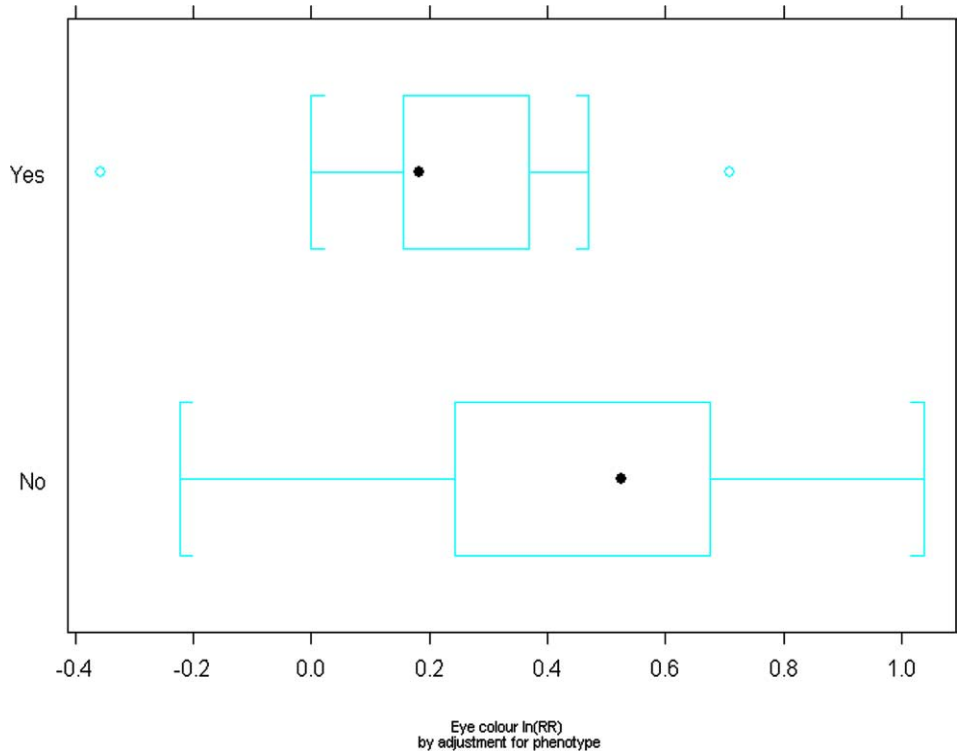

Fig. 9. "Blue *vs*. Black" eye colour Ln(RR) by adjustment for phenotype.

among the estimates was related to the country of the studies, like for intermittent sun exposure [2]. Meta-regression indicated that the estimates in the subgroup of studies coming from Australia, USA, Canada or UK (pooled RR = 1.73, 95% CI: 1.38, 2.18, with Chi-square $P < 0.001$) were lower ($P = 0.07$) than the ones obtained for the other countries (RR = 2.53, 95% CI: 1.79, 3.58, with Chi-square $P < 0.001$).

Even if adjustment for phenotype was not significant in explaining variability among the estimates, a reduction was observed in the pooled RR calculated on the estimates adjusted for phenotype. Pooled estimate on not adjusted estimates for phenotype was RR = 2.29 (95% CI: 1.61, 3.27; Chi-square $P < 0.001$) whereas the pooled RR on adjusted estimates is RR = 1.70 (95% CI: 1.49, 1.94) with not indication of heterogeneity ($P = 0.33$). Similar trends were observed previously for hair and eye colour, suggesting a correlation between these factors.

Rodenas [52] presented an adjusted estimate much lower than the crude one (OR = 4.2 and 95% CI 1.67, 10.57; OR = 0.50 and 95% CI 0.11, 2.18, for crude and adjusted estimates, respectively), and there was a suspicion of a type error. However these two ORs were not outliers and their weights were not large ($w = 1.77$ and 4.51, for adjusted and unadjusted estimates, respectively) therefore they had no considerable influence on the pooled estimates. In the paper published by Nelemans [53], it was not completely clear which reference categories were considered. In the first table that was published in their paper, only the highest category was indicated ("Light") and it was not obvious which was the reference category; in the second table they presented cases and controls from North Europeans and Middle Europeans and probably North Europeans were considered as "Light skin". If this hypothesis was correct this study should not be included in the meta-analysis, because classification of all North European people as fair skin subjects was considered too rough. However the weight of this study was not very big ($w = 10.42$) and the final results cannot change. Male estimates extracted from the paper published by Graham [45] were quite unstable because very few subjects were in the reference category; however its weight was also quite low ($w = 2.69$). Freedman [54] compared deaths from melanoma with non-cancer deaths, drawn from a database supported by two American national health institutes. Subjects were classified in "Fair" or "Other White" and they were defined "Fair skinned" if they were Caucasians and coming from Britain, Ireland, Germany, Scandinavia, Poland or other Northern European countries. Weight of the relative risk estimate published in this paper was really huge ($w = 435$) but the estimate was very low and not significant (RR = 1.01 and 95% CI 0.92, 1.11), therefore the decision to include this estimate was conservative. A further analysis was carried out excluding the four previously cited odd studies [45, 52–54]. Heterogeneity remained highly significant

($P < 0.001$) and the pooled RR was very similar to the one obtained in the main analysis (RR = 2.03 and 95% CI 1.71, 2.41). However, when we excluded another study [55], which presented a very high estimate (OR = 15.41 and 95% CI 7.82, 30.38) and it influenced heterogeneity, Chi-square decreased considerably ($P = 0.04$) and the pooled estimate remained highly significant (RR = 1.84 and 95% CI 1.63, 2.09). A further analysis was carried out including the four estimates published by Chen [13], for the four body sites, and the pooled RR did not show a significant change for "Light" *vs*. "Medium/Dark" skin colour: 2.02 (95% CI: 1.63; 2.51).

Analysis of publication bias, proposed by Copas and Shy, gave an indication of an overestimation of the risk for "Light" skin colour. However with eight more papers, *P*-value for publication bias was not any more significant ($P = 0.11$) and the new pooled RR still indicated "Light" skin colour as a significant risk factor (RR = 1.72 and 95% CI 1.39, 2.13). Similar indication was found with Egger's method ($P < 0.001$) and Begg's method ($P = 0.030$).

4. Discussion

In the two previous meta-analyses [1,2], naevi counts and sun exposure experiences have been investigated with all heterogeneity factors. This meta-analysis considered the remaining important risk factors for melanoma. It was decided to avoid the evaluation of risk factors mentioned in certain publications where highly contradictory evidence of an effect was reported, such as sunscreen [56] and oral contraceptives [57,58]. These two risk factors were investigated in two recently published meta-analyses [59,60] where no association with melanoma was found. Diseases, therapies or situations that may become big risk factors for melanoma, but that were studied only on very small populations, such as immunosuppressors and PUVA therapy [61] or ionising radiations [62], were not considered in this work. Personal history of melanoma was also not included in this meta-analysis because important studies estimated a very high risk of melanoma associated with a previous melanoma [63,64]. Such individuals are well known to be at high risk. It was decided to exclude socio-economic level from the meta-analysis because there was enough evidence that, at least a large proportion of this socio-economic gradient, could be explained by variations in sun exposure [41,65,66]. Diet was not considered, although various associations with dietary factors were suggested for melanoma, because the available information was very limited. Age and sex were considered as confounding factors. Individual phenotypic characteristics, including hair colour, colour of the iris and freckling are strongly related to sensitivity to ultraviolet (UV) light. Persons with a light complexion are considerably more photosensitive than persons who have dark hair, iris and skin colour, respectively. Constitutional UV sensitivity is, in turn, an important risk factor for malignant melanoma and for non-melanoma skin cancer in Caucasians. There is a clear overall pattern of association, *e.g.*, red-haired people tend to have freckles and be blue eyed, whereas black-haired people rarely have freckles and mostly are brown eyed. Several constitutional characteristics are highly inter-related, and possibly interact with each other in determining individual UV sensitivity and, ultimately, melanoma cancer risk. Thus, the individual characteristics mentioned above, and additionally the reaction of unprotected skin to mid-day summer sunlight ('Boston classification' according to Fitzpatrick) are often analysed as risk factors and important confounders, respectively, in epidemiological studies on skin cancer and melanoma. All these factors are related with the amount and type of cutaneous melanin. There are good evidences that there are at least two groups of melanins: eumelanins and pheomelanins [67]. Studies are on going to evaluate the role of the type of melanin in skin cancer risk (both melanoma and carcinomas) [68]. The relation between phenotypic characteristics makes difficult to assess their individual contribution to cancer risk [69,70]. However, in the Bliss study [15], individual subjects meta-analysis, hair, eye and skin colours appear largely independent and the authors discussed the possibility of combining them to demarcate high risk groups who can be targeted for prevention. Clearly hair and eye colours cannot be considered directly in a causal relationship with melanoma and are likely to be risk factors by virtue of their correlation with skin phenotype. Their evident association with melanoma may be because it is easier to have an indicative measure of hair and eye colour, compared to skin colour. They have a wide colour range in many populations whereas skin colour is difficult to measure and has a much narrower colour range. This makes it more difficult to obtain a reliable estimate of risk for skin colour. Moreover, if in ascertaining ability to tan, problems of recall bias and reliability arise, in the findings related to differences in eyes or hair colour definitions, it is more difficult to raise the question of misclassification bias. Therefore, relative risk estimates for the established host factors should be quite reliable [47].

As in the previous meta-analysis on sunburn history [2], we have shown in this work that latitude was an important factor to explain variability among relative risk estimates for high freckle density: studies conducted at higher latitudes presented higher risks for freckles and for sunburns history. This suggests that, at higher latitude, people with more freckles could have a higher risk of getting melanoma. In the previous paper on sunburn experiences, we discussed that sunburn could

correspond to the intermittent pattern of sun exposure and this may be much more strongly in people from higher latitudes than they do in people from lower latitudes, at least in Europe where many people have little regular exposure and increase sun exposure during holidays and recreational activities. At higher latitudes, sunburn is probably uncommon, unless a person takes holidays at lower latitudes whereas in lower latitudes sunburn is probably quite common even in people who have little opportunity for recreational sun exposure. That is if, as we could suspect, sunburn is a surrogate for intermittent pattern sun exposure (and possibly a better surrogate than other measures which are used) and it is a better surrogate in people living in higher latitudes than it is in people living in lower latitudes. The trend found for freckles, perhaps, is due to the fact that latitude and phenotypic characteristics, such as freckles and skin type, are confounded and that the primary interacting factor should be phenotypic characteristics and not latitude. However, while this is a reasonable postulate for studies done in Europe, it does not necessarily apply at all in Australia and North America.

On the subject of interaction of sun exposure with skin type, in causing skin cancer, interesting findings were published in Armstrong's paper [71]. In this context, it may be attractive to look extensively at modification of sun exposure effects on melanoma risk by some characteristics of subjects, such as skin type, number of naevi, number of freckles, based on the studies in which relevant results have been presented.

It is important to take into account that the apparent association of melanoma with some indicators of photodamage may be due to intensified medical surveillance in patients with a history of other cancers, a shared internal pathway of cancer induction and adverse effects of agents used in the treatment of non melanoma skin cancers [72]. A shared internal pathway of induction may be important in the association of actinic keratoses and photoageing with melanoma. Actinic keratoses, for example, are more common in light-skinned, light-haired, light-eyed individuals subjected to high levels of sun exposure. Because their skin has less protective pigment, they are the most susceptible to sunburn that is strongly associated with solar keratoses [73]. Strong association between degree of photoageing and lifetime sun exposure has also been found in extensive longitudinal studies conducted in Australia [113].

Similarly to Ford's meta-analysis, familial relative risk was found quite similar in all studies retrieved for this work, suggesting similar risks for family history even in completely different countries, which present a variability of 10-fold of incidence rates. This provides an indication for the hypothesis of independence between sun exposure and genetic susceptibility. However, Siskind [74] found a significant interaction between the effect of sun exposure on melanoma risk and familial susceptibility to melanoma. He suggested that melanoma may develop in a susceptible subset of the population who receives a threshold UV dose. Within families at relatively low genetic risk, cumulative sun exposure is likely to be a more important determinant of melanoma risk.

In these meta-analyses, we have shown that there are different phenotypic expressions of those at high risk of developing melanoma. Whiteman [75] and Rivers [76] recently suggested that melanoma may arise from at least two pathways, and perhaps the initiating factors differ for each. This is important because if a dual pathway for melanoma is supported by other investigations, public-health messages can be tailored to the population at risk. Clinically, the two phenotypic types at higher risk should be: light-skinned red heads, who are prone to freckles but with few melanocytic naevi, and others who may be of a darker skin complexion but with a substantial number of melanocytic naevi. Some preliminary studies of the environmental and phenotypic features, which looked at *TP53* melanoma [77] and mutations in the *BRAF* gene, support the dual pathway proposed by Whiteman for the development of melanoma: one related to chronic exposure to the sun, for melanomas of the extremities or face, and the other related to melanocyte instability, for melanoma of the trunk.

The melanocortin-1 receptor has a critical role in the type of melanin produced by melanocytes, and helps to some extent in the determination of hair colour. Variants in this protein increase the risk for melanoma. Further, this increased risk may be independent of skin complexion, suggesting that the risk conferred by variants in the melanocortin-1 receptor might be related to changes unrelated to visible differences in skin pigmentation phenotype. As Rivers suggests [76], the study of gene-environment interactions is clearly the next arena for epidemiological research into melanoma.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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Table 3
Definitions and classification for indicators of photodamage

First author (year)	Definitions	Classification
Bataille, 1998	Number of solar keratoses on left forearm: 10+	Pre-mal. and cancer les.
Bataille, 1998	Degree of solar elastosis: severe	Other indic. of act. damage
Dubin, 1990	Prior non-melanoma skin cancer or solar keratosis: yes	Pre-mal. and cancer les.
Frisch, 1996	Previous basal cell carcinoma: yes	Pre-mal. and cancer les.
Garbe, 1989	Actinic lentigines: moderate to large numbers	Other indic. of act. damage
Garbe, 1994	Actinic lentigines: many	Other indic. of act. damage
Green, 1986	Lentigines on arms: any	Other indic. of act. damage
Green, 1986	Actinic tumor on face: yes	Pre-mal. and cancer les.
Halpern, 1991	Actinic damage: severe	Other indic. of act. Damage
Holly, 1987	Previous skin cancer: yes	Pre-mal. and cancer les.
Holman, 1984	Cutaneous microphotograph (grade): 6+	Other indic. of act. Damage
Holman, 1984	History of non-melanocytic skin cancer: yes	Pre-mal. and cancer les.
Kaskel, 2001	Solar lentigo	Other indic. of act. Damage
Kaskel, 2001	Actinic keratosis	Pre-mal. and cancer les.
Lindelof, 1991 w.	Previous basal cell carcinoma (BCC): yes	Pre-mal. and cancer les.
Lindelof, 1991 m.	Previous basal cell carcinoma (BCC): yes	Pre-mal. and cancer les.
Marghoob, 1995	Patients who had a BCC and/or squamous cell carcinoma (SCC): yes	Pre-mal. and cancer les.
Marrett, 1992	Splotchy freckles: yes	Other indic. of act. damage
Moore, 1997	Previous skin cancer: yes	Pre-mal. and cancer les.
Naldi, 2000	Solar lentigines	Other indic. of act. Damage
Osterlind, 1988	Cutaneous microphotograph (grade): 4+	Other indic. of act. damage

Appendix A

See Table 3.

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